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(54) **BIOFILM EXTRACELLULAR POLYSACCHARIDE SOLVATING SYSTEM**

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See application file for complete search history.

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(57) **ABSTRACT**

The invention provides a solvating system for the removal of biofilms which solvates the extracellular polysaccharide matrix holding it to a surface. The aqueous solvating system comprises water, a metal ion sequestering agent, and a solvating agent for an extracellular polysaccharide matrix, which is gentle enough to be used directly on human tissues, but which may also be used on hard or soft non-tissue surfaces to breakdown, and/or remove biofilms.

25 Claims, No Drawings

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BIOFILM EXTRACELLULAR POLYSACCHARIDE SOLVATING SYSTEM

CROSS-REFERENCE TO RELATED APPLICATION

This application is a Divisional of application Ser. No. 11/431,495 filed May 10, 2006, the disclosure of which is incorporated by reference.

THE FIELD OF THE INVENTION

The present invention relates generally to the field of biofilm removal and more specifically to a solvating system for the solvation and removal of biofilms. The solvating system may be used on a variety of affected surfaces, including human or animal tissue, medical devices, water systems, and the like. The solvating system is especially beneficial for use on human tissue to remove biofilms which cause chronic conditions such as rhinosinusitis.

BACKGROUND OF THE INVENTION

Biofilms are formed by bacteria in aqueous environments, which interact with the surfaces to which they are exposed to form surface colonies and films which continue to adhere to the surfaces and grow. More specifically, the bacteria produce extensive exopolysaccharide or extracellularpolysaccharide polymers (EPS or ECPS) that keep them attached to the surfaces and form living films thereon, frequently called "biofilms". These biofilms can be formed on a variety of surfaces, including human tissues, medical devices, dental office equipment, counters, pipes and the like. Biofilms coat the surface and become a living colony for the continued proliferation of microorganisms, and protection of the microorganisms from removal and from conditions which might destroy the microorganisms. Biofilms are much more difficult to remove than bacteria in the plaktonic state, and the bacterial contamination of the biofilms from surfaces or tissue are thus much more difficult to eliminate. Biofilms in this state are extremely resistant to many antibiotics and biocides.

When present on human tissues, biofilms can cause chronic conditions from which many persons today suffer. Such conditions include rhinosinusitis, where biofilms are attached within the nasal passages and sinuses, infiltrating and protecting the underlying pathogenic bacteria and preventing them from being dislodged from their surfaces, and immune system disorder symptoms where biofilms have coated bodily tissues and surfaces such as joints or nerves in a manner which impairs the normal function thereof. Additionally, enclosure of implants or surgical appliances with biofilms may lessen their effectiveness.

Previous strategies for removal of biofilms have focused on both removal and destruction of bacteriums in the biofilm. Products for such cleansing, such as biocides, disinfectants and the like for use in such areas may be caustic and employ agents that can damage human skin, and especially non-dermal human tissues upon contact and therefore cannot be used to remove biofilms from human orifices and tissues. Methods of cleaning and disinfecting such surfaces effectively for biofilms may also involve large dosages, and long periods of contact with the surface, e.g., soaking biofilm contaminated surfaces for 12-24 hours, which is impractical for preoperative and postoperative situations and for many surfaces and devices as well as being impossible for use on or with most contaminated human tissues.

Methods of removal of biofilms from human tissues such as sinuses to flush them from the system have included mechanical debridement of the tissues and/or surgical opening of sinuses to allow for drying and subsequent removal of the biofilm. Such methods damage the tissues and require healing periods, and further present opportunities for new bacteria to contact the surfaces and cause infections and new placement of biofilms. Antibiotics have also been attempted but, while they are effective against plaktonic bacteria, they have been only marginally effective against biofilms, and then only when administered in large dosages, which may be otherwise undesirable for the patient or living tissues.

It would be desirable to have a solvating system for removing biofilms from human tissues which would meet biocompatibility requirements for contact with human tissue, and yet be effective in removal of such biofilms from tissues and bodily orifice linings such as nasal orifices, sinuses, oral tissues, for removal from implants or other appliances attached to bodily tissues and the like. Such desirable solvating systems would preferably be effective in small dosages for short periods of application. It would also be desirable for such solvating system to be further useful to dislodge biofilms attached to non-tissue surfaces in environmental locations such as medical devices and water systems, dental equipment and the like.

It has now been discovered that a solvating system comprising an alkali, metallic, or metal ion sequestering agent and a solvent or surfactant is surprisingly effective in removal of biofilms such as polysaccharides from human tissue while being gentle enough for application directly onto such tissues.

SUMMARY OF THE INVENTION

The invention provides a solvating system for the breakdown and/or removal of biofilm matrices from human tissue surfaces and nonhuman surfaces.

More specifically, the invention provides an aqueous solvating system for the breakdown of the biofilm's extracellular polysaccharide matrix, and consequent detachment/removal of biofilms from the surface to which it is attached or adhered. The solvating system of the invention comprises a metal ion sequestering agent and a solvating agent for the extracellular polysaccharide matrix selected from a solvent or a surfactant.

In one embodiment, the invention includes an aqueous solvating system comprising water or saline, a metal ion sequestering agent and a solvating agent selected from the group consisting of a solvent and a surfactant.

In another embodiment, the solvating system of the invention comprises metal ion sequestering agent selected from the group consisting of a mild acid having a molarity of at least about 0.05 molar.

In one embodiment, the metal ion sequestering agent is a mild acid having a molarity of at least about 0.05 molar wherein the metal ion is selected from alkali metals, alkaline earth metals, and iron.

In another embodiment, the solvating system comprises a solvating agent for the extracellular polysaccharide matrix selected from the group consisting of anionic surfactants, nonionic surfactants, cationic surfactants and zwitterionic surfactants.

The invention also provides a method of use for the solvating system comprising delivery to the affected location by power spray or lavage.

These terms when used herein have the following meanings.

1. The term "sequestering agent" means a chemical that will combine with another material, especially a metal ion, to prevent the material from coming out of solution.

2. The term "metal ion sequestering agent" means a sequestering agent that will combine with metal ions such as iron, alkali metals, alkaline earth metals, and the like to keep the metals in solution. In order of increasing atomic number the alkaline earth metals are beryllium, magnesium, calcium, strontium, barium, and radium. Alkali metals include sodium, potassium, rubidium, cesium, and francium.

3. The terms "attached" and "adhered" as used herein means that the biofilm is established on the surface which it coats or covers, and that the biofilm has some resistance to removal from the surface, whether the surface is living tissue or a nonliving surface. As the nature of this relationship is complex and poorly understood, no particular method of adherence or attachment is intended by such usage.

4. The term "solvating" means to form a solution consisting of the solvent and the solvate.

5. The term "removal of biofilms" means that at least a significant amount of the biofilm present on a surface is placed into suspension and no longer resides on the surface.

All weights, amounts and ratios herein are by weight, unless otherwise specifically noted.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The following detailed description describes certain embodiments and is not to be taken in a limiting sense. The scope of the present invention is defined by the appended claims.

The invention provides an aqueous solvating system for the breakdown of the biofilm's extracellular polysaccharide matrix, and consequent detachment or removal of biofilms from the surface to which it is attached or adhered. The solvating system of the invention comprises a metal ion sequestering agent and a solvating agent for the extracellular polysaccharide matrix selected from a solvent or a surfactant.

The invention is biocompatible, and may be used directly on human tissue as well as other non-living surfaces. It is advantageous in that it contains no biocides which could be potentially harmful to human tissues.

Another advantage of the solvating system invention is that it is low viscosity which makes for easy delivery to the desired surface by means of lavage, misting, spray application, mopping, administering in droplets, and also easy removal by subsequently flushing, rinsing, and/or draining from orifices such as nasal passages or from other surfaces. In one embodiment, the solvating system has a pH of from greater than about 5 to about 8.5.

The sequestering agent is a metal ion sequestering agent, generally a mild acid of high molarity. Useful acids include citric acid, mandelic acid, 2-ketoglutaric acid, acetic acid, iminodiacetic acid, mucic acid, glycolic acid, fumaric acid, lactic acid, aspartic acid, phosphoric acid, pyruvic acid, chloroacetic acid, oxalic acid, oxamic acid, malic acid, dichloroacetic acid, phenylacetic acid, benzylic acid, maleic acid, succinic acid, chloromandelic acid, glutamic acid, nitrilotriacetic acid, boric acid, adipic acid, formic acid, glucuronic acid, salicylic acid, benzoic acid, benzoyl acid, formic acid, phthalic acid, ketopimelic acid, and hydrochloric acid.

Applicable metal ions which may be sequestered include alkali metals, alkaline earth metals, iron, and the like. In one embodiment the metal ion sequestering agent is an alkaline earth metal or alkali metal sequestering agent. The sequestering agent generally has a molarity of at least about 0.05 molar, preferably from about 0.05 to about 0.35 molar.

The solvating system further includes a solvating agent selected from a surfactant or solvent. Useful solvating agents include surfactants such as alkyl sulfates, alkyl sulfonates and aryl sulfonates. The surfactant is generally present in a strength of from about 0.001 to about 0.69 molar, preferably from about 0.025 to about 0.130 molar, and in an amount of from about 0.5% to about 20% of the weight of the solution.

The solvating agent may be selected from various surfactants, such as anionic surfactants, nonionic surfactants, cationic surfactants and zwitterionic surfactants. Useful anionic surfactants include but are not limited to, sodium chenodeoxycholate, N-lauroylsarcosine sodium salt, lithium dodecyl sulfate, 1-octanesulfonic acid sodium salt, sodium cholate hydrate, sodium deoxycholate, sodium dodecyl sulfate, and sodium glycodeoxycholate. Useful cationic surfactants include but are not limited to hexadecylpyridinium chloride monohydrate, and hexadecyltrimethylammonium bromide. Useful nonionic surfactants include but are not limited to polyoxyethyleneglycol dodecyl ether, N-decanoyl-N-methylglucamine, Digitonin, n-dodecyl B-D-maltoside, octyl B-D-glucopyranoside, octylphenol ethoxylate, polyoxyethylene (8) isooctyl phenyl ether, polyoxyethylene sorbitan monolaurate, and polyoxyethylene (20) sorbitan monooleate. Useful zwitterionic surfactant include but are not limited to 3-[(3-cholamidopropyl) dimethylammonio]-2-hydroxy-1-propane sulfonate, 3-[(3-cholamidopropyl) dimethylammonio]-1-propane sulfonate,3-(decyldimethlammonio) propanesulfonate inner salt, and N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate. In one embodiment, the surfactant is sodium lauryl sulfate.

While not wishing to be bound by theory, it is believed that the metal ion sequestering material removes the ion which bridges the extracellular polysaccharide matrix and binds the polymer chains together. The solvating agent then first surrounds the unbound polymers and suspends them, breaking down the matrix, and subsequently solvates the unbound polymers, bringing them into solution where they can be easily flushed from the tissues or surfaces with the aqueous solvating solution.

Where desirable to both remove the biofilm and destroy the microorganisms contained therein, the solvating system of the invention may further include medicaments such as antibiotics, which will be much more effective against the microorganisms present after the extracellular polysaccharide matrix has been broken down into unbound polymers, suspended and/or solvated.

The solvating system may further include a buffer in order to provide a solution at the proper pH for contacting human tissue. Where desirable, the buffer may comprise up to about 25% of the active ingredients of the solution. Useful buffers include, but are not limited to potassium chloride, glycine, potassium hydrogen phthalate, sodium acetate, potassium hydrogen phthalate, barbitone sodium, and sodium citrate.

Where treatment of tissues is also desirable, the solvating system of the invention may include further pharmaceutical agents in appropriate dosages such as analgesics, steroids, and the like.

For comfort and ease of use in human patients, the solvating system may further include flavoring agents and sweetening agents including but not limited to, oil of peppermint, spearmint, wintergreen, clove, eucalyptus, cinnamon, lemon, lime and orange, cherry, sucrose, lactose, maltose, sorbitol, xylitol, sodium cyclamate, saccharine, and the like.

Additional adjuvants may include antioxidants, buffering agents, coloring agents, and the like, in amounts that will not substantially interfere with the salvation of the extracellular polysaccharide and removal of the significant amounts of the biofilm.

Although specific embodiments have been illustrated and described herein for purposes of description of the preferred embodiment, it will be appreciated by those of ordinary skill in the art that a wide variety of alternate and/or equivalent implementations calculated to achieve the same purposes may be substituted for the specific embodiments shown and described without departing from the scope of the present invention. Those with skill in the chemical, mechanical, electro-mechanical, electrical, pharmacological and computer arts will readily appreciate that the present invention may be implemented in a very wide variety of embodiments. This application is intended to cover any adaptations or variations of the preferred embodiments discussed herein. Therefore, it is manifestly intended that this invention be limited only by the claims and the equivalents thereof.

What is claimed is:

1. A method for the breakdown of a biofilm extracellular polysaccharide matrix, and for detachment or removal of the biofilm from a surface to which it is attached or adhered, which method comprises applying an aqueous solvating system solution to a biofilm on human or animal nasal passage or sinus tissue, or on a prosthetic system attached to such tissue, wherein said solution comprises water, an amount of metal ion sequestering agent and an amount of solvating agent for the extracellular polysaccharide matrix effective to break down such matrix and to detach or remove such biofilm from such surface, said solvating agent comprises a cationic or zwitterionic surfactant, and said solution has a pH greater than 5 and does not contain biocide harmful to such tissue.

2. A method according to claim **1** wherein said solution is applied to nasal passage tissue.

3. A method according to claim **1** wherein said solution is applied to sinus tissue.

4. A method according to claim **3** wherein said solution is applied to nasal passages or sinuses of persons with rhinosinusitius.

5. A method according to claim **1** wherein said solution is applied in the form of a spray, liquid, or gel.

6. A method according to claim **1** further comprising removing said solution by rinsing.

7. A method according to claim **1** further comprising removing said solution by allowing said solution to drain out of said tissue, by flushing or by aspiration.

8. A method according to claim **1** wherein said metal ion sequestering material removes an ion which bridges the biofilm extracellular polysaccharide matrix and binds polymer chains together.

9. A method according to claim **1** wherein said metal ion sequestering agent is a mild acid having a molarity of at least about 0.05 molar.

10. A method according to claim **1** wherein said metal ion sequestering agent has a molarity from about 0.05 to about 0.35 molar.

11. A method according to claim **1** wherein said metal ion sequestering agent comprises mandelic acid, 2-ketoglutaric acid, acetic acid, iminodiacetic acid, mucic acid, glycolic acid, fumaric acid, lactic acid, aspartic acid, phosphoric acid, pyruvic acid, chloroacetic acid, oxalic acid, oxamic acid, malic acid, dichloroacetic acid, phenylacetic acid, benzylic acid, maleic acid, succinic acid, chloromandelic acid, glutamic acid, nitrilotriacetic acid, boric acid, adipic acid, formic acid, glucuronic acid, salicylic acid, benzoic acid, benzoyl acid, phthalic acid, ketopimelic acid or hydrochloric acid.

12. A method according to claim **1** wherein said metal ion sequestering agent comprises citric acid.

13. A method according to claim **1** wherein said metal ion is selected from alkali metals, alkaline earth metals, and iron.

14. A method according to claim **1** further comprising a buffer.

15. A method according to claim **14** wherein said buffer comprises potassium chloride, glycine, potassium hydrogen phthalate, sodium acetate, potassium hydrogen phthalate, barbitone sodium or sodium citrate.

16. A method according to claim **14** wherein said metal ion sequestering agent comprises citric acid and said buffer comprises sodium citrate.

17. A method according to claim **14** wherein said buffer comprises up to about 25% of said solution.

18. A method according to claim **1** wherein said solvating agent is a cationic surfactant.

19. A method according to claim **1** wherein said solvating agent comprises hexadecyltrimethylammonium bromide.

20. A method according to claim **1** wherein said solvating agent is a zwitterionic surfactant.

21. A method according to claim **1** wherein said solvating agent comprises 3-[(3-cholamidopropyl)dimethylammonio]-2-hydroxy-1-propane sulfonate, 3-[(3-cholamidopropyl) dimethylammonio]-1-propane sulfonate, 3-(decyldimethlammonio) propanesulfonate inner salt or N-dodecyl-N,N-dimethyl-3-ammonio-1-propanesulfonate.

22. A method according to claim **1** wherein said solvating agent is present in said solution in a strength of about 0.001 to about 0.69 molar.

23. A method according to claim **1** wherein said solvating agent is present in said solution in a strength of about 0.025 to about 0.13 molar.

24. A method according to claim **1** wherein said solvating agent is about 0.5 to about 20 weight percent of said solution.

25. A method according to claim **1** wherein said solvating system has a pH up to about 8.5.

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